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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/001,221	10/30/2001	Thomas J. Schall	10709-014	2004

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EXAMINER
CANELLA, KAREN A

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 01/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/001,221	SCHALL ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *69-72 and 75-106* is/are pending in the application.

4a) Of the above claim(s) *76-78 and 93-96* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *69-72,75,79-92 and 97-106* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claim 69 has been amended. Claims 73 and 74 have been canceled. Claims 89-106 have been added. Claims 69-72 and 75-106 are pending. Claims 76-78, and 93-96, drawn to non-elected species are withdrawn from consideration. Claims 69-72, 75, 79-92, 97-106 are under consideration.

2. Applicant has submitted a new set of claims on August 19, 2005 in response to "the office action of January 8, 2004". However, applicant is not entitled to consideration of as supplemental claim set over the claims submitted September 7, 2004 for two reasons. The first reason is that applicant has already responded to the Office action of January 8, 2004 by the response filed March 8, 2004. Secondly, the claims of August 19, 2005 list claims 69-88 as "new" but claims 69-88 were introduced in the amendment filed March 8, 2004. The amendment of September 7, 2004 subsequently amended claim 69, canceled claims 73 and 74 and added claims 89-106, therefore the status of the claims listed in the amendment filed August 19, 2005 is incorrect. Secondly, the entry of a supplemental response will not be entered as a matter of right. See section 714.03(a) of the M.P.E.P. which states that conditions for entry of a supplemental response are limited to

(A) Cancellation of a claim(s);
(B) Adoption of the examiner suggestion(s);
(C) Placement of the application in condition for allowance;
(D) Reply to an Office requirement made after the first reply was filed;
(E) Correction of informalities (e.g., typographical errors); or
(F) Simplification of issues for appeal.
(ii) A supplemental reply will be entered if the supplemental reply is filed within the period during which action by the Office is suspended under § 1.103(a) or (c).

Since none of the above conditions have been met, the amendment filed August 19, 2005 will not be entered.

3. Text of Title 35, U.S. Code, not found in this action can be found in a previous action.

4. Claims 89-92 and 97-106 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kedar et al (Advances in Cancer Research, 1992, Vol. 59, pp. 245-322) in view of Bystryn (WO 98/33520) and Mohamadzadeh et al (Archives of Dermatological Research, 1997, Vol. 289, pp. 435-439) and Orlofsky et al (Cytokine, March 2000, Vol. 12, pp. 220-228).

Kedar et al teach that preclinical and clinical studies indicate that antigenicity of a tumor and the capacity to mobilize a T-cell response are required for successful immunotherapy(page 254, lines 3-5). Kedar et al teach that infiltrating macrophage, neutrophils and eosinophils are present in regressing tumors indicating that said infiltrating cells are mobilized by lymphokines released from the antigen-specific T-cells. (page 255. lines 5-11). Kedar et al teach that said cells are contributing to the therapeutic effect (page 256, lines 1-2). Kedar et al teach stealth liposomes which can evade the reticuloendothelial system thereby achieving a prolonged circulation time and enhanced accumulation in tumors in various body compartments (page 266, lines 10-20). It is noted that said stealth liposomes are taught by Kedar et al to be smaller than 0.1 um, and thus fulfill the specific embodiment of claim 80 drawn to a microsphere. Kedar et al teach that administration of biological modifiers such as cytokines by encapsulation in liposomes bypasses the need for continuous infusion or frequent bolus administrations to counteract the short plasma half-lives of cytokines or other biological response modifiers (page 265, lines 1-6 under the heading "New Methods for Delivery of cytokines and Other Biological Response Modifiers"). Kedar also teach that tumor antigens encapsulated in liposomes can improve the immunogenicity of said tumor antigen in human patients and that administration of the tumor antigen together with cytokines and improved adjuvants demonstrate increased anti-tumor efficacy in experimental animals (page 287, lines 16-35 under the heading "Active Specific Immunotherapy"). Kedar et al teach that treatment with combinations of cytokines differing in their mode of action, each at subtoxic doses may improve the therapeutic index (page 260, lines 5-7, under the heading "Cytokine Combinations"). Kedar et al do not specifically teach C10 as a biological response modifier, or an encapsulated liposome comprising a chemokine, adjuvant and a tumor antigen.

Bystryn (WO 98/33520) teaches pH sensitive liposomes (page 2, line 21 to page 3, line 18) and encapsulated vaccine containing immunomodulators (page 5, lines 3-7 and page 6, line 1 to page 7, line 2). Bystryn teaches oral, inhalation, intradermal, subcutaneous, intramuscular, intravenous and topical administration of the vaccines (page 30, lines 4-12). Bystryn teaches that pH sensitive liposomes are taken up by antigen-presenting cells (page 3, lines 5-8) .

Mohamadzadeh et al (Archives of Dermatological Research, 1997, Vol. 289, pp. 435-439) teach that both dendritic and Langerhan's cells are sources of the C10 chemokine for the recruitment of T cells and cytokines involved in initiation of inflammatory events (page 438, second column, lines 28-32) in addition to the processing and presentation of protein antigens and the induction of primary T cell response

Orlofsky et al (Cytokine, March 2000, Vol. 12, pp. 220-228) teach that the murine chemokine C10 modulated immune reactions of the Th2 type (page 225, second column, lines 9-11). Orlofsky et al teach that subsequent development of a Th2 response is ineffective at suppressing C10 expression (page 225, second column, lines 14-17). Orlofsky et al conclude that the decisive period for C10 regulation would thus be before C10 expression is induced and therefore during the generation of early inflammatory signals (page 225, second column, lines 17-21). Orlofsky et al teach that C10 is chemotactic for macrophages and T and B lymphocytes and that C10 acts to maintain modes of cellular interactivity previously initiated by the more transient chemokines such as MIP-1 alpha, or that C10 specifically attracts one or more T cell subsets.

It would have been prima facie obvious at the time the claimed invention was made to use C10 for the immunomodulator in the stealth liposomes taught by Kedar et al. It would have been further obvious to combine C10 with a tumor antigen, an additional chemokine and an adjuvant in said liposome for a prolonged circulation time in a patient and to administer said liposomes by oral, inhalation, intradermal, subcutaneous, intramuscular, intravenous and topical routes. One of skill in the art would have been motivated to do so by the teachings of Kedar et al on the accumulation of said stealth liposomes at the tumor site; and the teachings of Orlofsky et al on the maintenance of the Th2 response by C10 and the teachings of both Orlofsky et al and Mohamadzadeh et al on the recruitment by C10 of T cells and cytokines involved in the inflammatory response. One of skill in the art would also have been motivated to combine the

liposome encapsulated C10 with the tumor antigen because Kedar et al teaches that encapsulation of tumor antigens within liposomes can improve the immunogenicity of said tumor antigen. One of skill in the art would have been motivated to combine the MCK-2 chemokine with an additional chemokine in order to exert an additive or synergistic effect. It is noted that the encapsulation of both the C10 chemokine and the tumor antigen within the liposome fulfill the specific embodiment of claim 75 drawn to the composition wherein the chemokine an the antigen are linked because occupying the same interior space of a liposome is a linkage between the chemokine and the tumor antigen. One of skill in the art would be motivated to further encapsulate the adjuvant by the teachings of Bystryn et al. Furthermore, one of skill in the art would be motivated to prepare sterile preparations of the liposome encapsulated pharmaceuticals in order to preserve the shelf life of said compositions and in order to prevent contamination with a pathogenic agent.

5. Claims 69-72 and 79-92 and 97-106 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kedar et al (Advances in Cancer Research, 1992, Vol. 59, pp. 245-322) in view of Bystryn (WO 98/33520) and Saederup et al (PNAS, Sep 1999, vol. 96, pp. 10881-10886).

Kedar et al teach that preclinical and clinical studies indicate that antigenicity of a tumor and the capacity to mobilize a T-cell response are required for successful immunotherapy(page 254, lines 3-5). Kedar et al teach that infiltrating macrophage, neutrophils and eosinophils are present in regressing tumors indicating that said infiltrating cells are mobilized by lymphokines released from the antigen-specific T-cells. (page 255. lines 5-11). It is noted that said stealth liposomes are taught by Kedar et al to be smaller than 0.1 um, and thus fulfill the specific embodiment of claim 80 drawn to a microsphere. Kedar et al teach that said cells are contributing to the therapeutic effect (page 256, lines 1-2). Kedar et al teach stealth liposomes which can evade the reticuloendothelial system thereby achieving a prolonged circulation time and enhanced accumulation in tumors in various body compartments (page 266, lines 10-20). Kedar et al teach that administration of biological modifiers such as cytokines by encapsulation in liposomes bypasses the need for continuous infusion or frequent bolus administrations to counteract the short plasma half-lives of cytokines or other biological response modifiers (page

265, lines 1-6 under the heading "New Methods for Delivery of cytokines and Other Biological Response Modifiers"). Kedar also teach that tumor antigens encapsulated in liposomes can improve the immunogenicity of said tumor antigen in human patients and that administration of the tumor antigen together with cytokines and improved adjuvants demonstrate increased anti-tumor efficacy in experimental animals (page 287, lines 16-35 under the heading "Active Specific Immunotherapy"). Kedar et al teach that treatment with combinations of cytokines differing in their mode of action, each at subtoxic doses may improve the therapeutic index (page 260, lines 5-7, under the heading "Cytokine Combinations"). Kedar et al do not specifically teach Mck-2 as a biological response modifier, or an encapsulated liposome comprising a chemokine, adjuvant and a tumor antigen.

Bystryn (WO 98/33520) teaches pH sensitive liposomes (page 2, line 21 to page 3, line 18) and encapsulated vaccine containing immunomodulators (page 5, lines 3-7 and page 6, line 1 to page 7, line 2). Bystryn teaches oral, inhalation, intradermal, subcutaneous, intramuscular, intravenous and topical administration of the vaccines (page 30, lines 4-12). Bystryn teaches that pH sensitive liposomes are taken up by antigen-presenting cells (page 3, lines 5-8) .

Saederup et al (PNAS, Sep 1999, vol. 96, pp. 10881-10886) teach that Mck-1/Mck-2 are responsible for promoting host leukocyte chemotaxis and may be responsible for attracting monocytes and macrophage as well (abstract, lines 15-18). Saederup et al teach that both MCK-1 and MCK-2 have the same chemokine domain but that MCK-2 contains an additional 199 amino acid sequence as a novel carboxyl terminus resulting form alternative RNA splicing (page 10881, second column, lines 8-13). Saederup et al teach that the observed data indicate that MCK-1 can recruit and activate monocytes or macrophages (page 10885, first column, lines 7-12). Saederup et al teach that MCK-1/MCK-2 mutant cannot sustain an inflammation relative to non-mutated MCK-1/MCK-2 consistent with the role of maintaining monocyte migration (page 10886, lines 36-40).

It would have been prima facie obvious at the time the claimed invention was made to use C10 for the immunomodulator in the stealth liposomes taught by Kedar et al. It would have been further obvious to combine MCK-2 with a tumor antigen, an additional chemokine, and an adjuvant in said liposome for a prolonged circulation time in a patient and to administer said liposomes by oral, inhalation, intradermal, subcutaneous, intramuscular, intravenous and topical

routes. One of skill in the art would have been motivated to do so by the teachings of Kedar et al on the accumulation of said stealth liposomes at the tumor site and the benefits of administering combinations of cytokines; and the teachings of Kedar et al on the therapeutic effect associated with recruitment of macrophage and monocytes to the tumor site and the teachings of Saederup et al on the recruitment of macrophage and monocytes by MCK-1/MCK-2. One of skill in the art would conclude that MCK-1 and MCK-2 can be used interchangeably because both MCK-1 and 2 contain the same chemokine domain and because mutation of either MCK-1 or MCK-2 can abrogate inflammation relative to the wild type. One of skill in the art would also have been motivated to combine the liposome encapsulated MCK-2 with the tumor antigen because Kedar et al teaches that encapsulation of tumor antigens within liposomes can improve the immunogenicity of said tumor antigen. One of skill in the art would have been motivated to combine the MCK-2 chemokine with an additional chemokine in order to exert an additive or synergistic effect. It is noted that the encapsulation of both the MCK-2 chemokine and the tumor antigen within the liposome fulfills the specific embodiment of claim 75 drawn to the composition wherein the chemokine an the antigen are linked because occupying the same interior space of a liposome is a linkage between the chemokine and the tumor antigen. One of skill in the art would be motivated to further encapsulate the adjuvant by the teachings of Bystryn n et al. Furthermore, one of skill in the art would be motivated to prepare sterile preparations of the liposome encapsulated pharmaceuticals in order to preserve the shelf life of said compositions and in order to prevent contamination with a pathogenic agent.

6. Applicant argues that Kedar et al does not provide motivation for combining references which teach chemokines (page 11 of the response) as opposed to cytokines. This has been considered but not found persuasive. One of skill in the art would understand that a chemokine is a pro-inflammatory cytokine and thus encompassed in the family of cytokines

Applicant argues in the middle of page 13 that the instant claims are based on the unexpected result imparted by the use of mC10 or vMCK-2 of the instant invention. Applicant argues that one of skill in the art would not have reasonably expected that a murine chemokine and a chemokine encoded by a mouse virus would have the capacity to trigger primate antigen-presenting cells. this has been considered but not found persuasive. Saederup et al (cited in the

previous Office action) teaches that a chemokine encoded by MCK-2 exerted an effect on cells bearing the human chemokine receptor CCR3 and the human macrophage line was also responsive to MCK-1 (abstract). Thus, it appears that chemokines can exert chemoattractant activity in homologous hosts. Further, the instant claims are product claims and therefore not limited by intended use in a human.

7. All other rejections and objections as stated in the previous Office action are withdrawn in light of applicant's amendments.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571)272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.

12/29/2005

KAREN A. CANELLA PH.D
PRIMARY EXAM